3.1. HISTORICAL ASPECT

According to the Greeks, “the disease of jaundice gets its name (icterus) from an animal of yellow colour. The disease occurs after prolonged ingestion or after the drinking of purgative drugs that remains within the body without being driven off. Symptomatic jaundice is the change to a yellow colour which first appears and is particularly noticeable in the whites of the eyes, the hollow of the soles, and the veins under the tongue. Moreover, the bowel fails to move, or whitish and clay stools occur and the urine is thick and saffron coloured. There is also a bitter taste in the mouth, thirst, loss of appetite, itching and dryness of the body, often the liver is swollen.”

Five centuries BC Hippocrates noted that “in jaundice, it is a bad sign if the liver hardens”. Although he had almost certainly recognized the hard, irregular liver and jaundice accompanying metastatic liver disease, it is true that in biliary tract obstruction long periods of jaundice accompanied by a palpable liver and compromise liver function are associated with an increase in morbidity and mortality after operation.

Pain, jaundice, and fever with rigors occurring together constitute the Charcot’s triad and indicate acute cholangitis. In 1877, he published this classical triad as typical findings of common bile duct stone.

The finding of a palpable gall bladder in the presence of obstructive jaundice suggests malignant obstruction to the biliary tree (Courvoisier’s law) and is most commonly due to carcinoma of the head of the pancreas. However, failure to palpate the gallbladder does not necessarily exclude malignant disease. In addition, it is possible to have a palpable distended gallbladder in the presence of gallstones where one obstructs the common bile duct and another is impacted in Hartmann’s pouch or cystic duct resulting in an empyema (or mucocele) of the gall bladder. Courvoisier was the first to remove a stone successfully from the common bile duct on 21st January 1890. He published his finding “of 187 cases, a shrivelled gall bladder was found in 70/87 with stones in common bile duct and distention in 92/100 from other causes.”

Occurrence of renal failure was first described by Clairmont and Von Haberer, in 1911, after surgery of obstructive jaundice in five patients. All of them died from acute renal failure. Since then many reports have been published regarding hepatorenal syndrome including pathogenesis of acute renal failure. The exact mechanism is not yet clearly understood.
2.2. RENAL DYSFUNCTION IN OBSTRUCTIVE JAUNDICE

Many studies have strongly suggested that there is a close association between liver and kidney disease. The term “hepatorenal syndrome” has been used to describe association between kidney and liver disease in patients dying of uraemia after biliary tract surgery or acute liver failure. Although jaundice is not a prerequisite for this condition, there is an incidence of acute renal failure after surgery in patients with obstructive jaundice. The term “hepatorenal syndrome” has since been redefined and is now reserved for patients with liver disease who develop renal dysfunction in the absence of any other known cause of renal failure. In contrast to renal failure associated with acute tubular necrosis, the hepatorenal syndrome is characterized by the functional nature and inherent reversibility of the renal disorder which has been suggested or proved by the virtual absence of abnormalities on light microscopy in the post-mortem kidneys, by the disappearance after death of vasospastic changes demonstrated during life with angiography, and by occasional spontaneous recoveries from the complication. The kidneys of patients dying from acute renal failure showed histopathological changes similar to those observed in hypovolaemic shock. Good renal function has been achieved in kidneys procured from donors with hepatorenal syndrome, and conversely, renal function has recovered in patients with hepatorenal syndrome after successful orthotopic liver transplantation.

3.2.a. RENAL FUNCTION AND PATHOGENESIS OF RENAL FAILURE IN OBSTRUCTIVE JAUNDICE

The pathological changes within the kidney following the development of renal failure are quite non-specific and vary from relatively few histological changes to acute tubular necrosis, with glomerular and peritubular fibrin deposition. A number of factors have been implicated as etiology of renal dysfunction. The factors that have been implicated are renal haemodynamics and body fluid disturbances, bacterial translocation from gut, endotoxaemia, disturbances of coagulation, decreased reticuloendothelial phagocytic capacity and hyperbilirubinaemia.

Alteration in renal blood flow or glomerular filtration rate (GFR) in obstructive jaundice has been addressed by many investigators, but remains controversial. In an experiment of bile duct ligation in dogs, Dawson observed that renal blood flow and glomerular filtration rate remained unchanged. This was supported by Zambraski and Dunn’s study. But some other studies reported mild degree of reduction in renal blood flow and glomerular filtration rate. In addition to possible changes in total renal blood flow, intrarenal cortical distribution of blood flow has been shown to be altered after bile duct ligation.
Bomzone and Kew\textsuperscript{21} concluded that catecholamines, rather than the renin and angiotensin system mediated the decrease in renal blood flow and redistribution of blood flow away from the outer cortex. However, it has been shown that renal nerve ablation does not prevent the decrease in renal blood flow after bile duct ligation\textsuperscript{6}. Change in intrinsic vascular reactivity could result in enhanced vascular tone and decreased renal flow, though sympathetic tone or catecholamine levels may not be increased. These effects suggest that any effect of jaundice or the renal vascular response to norepinephrine may be modulated by a separate effect on renal prostaglandin. There are similar findings in bile duct ligated experimental dogs where there was significant increase in renal production of prostaglandin E\textsubscript{2} and prostaglandin I\textsubscript{2} \textsuperscript{22}. These studies have found normal renal blood flow and GFR after bile duct ligation but administration of indomethacin caused a decrease in prostaglandin production resulting in a marked decrease in both renal blood flow and GFR. Zambraski and Dunn\textsuperscript{22} have noted redistribution of cortical blood flow with a relative increase in superficial cortical flow after prostaglandin inhibition with indomethacin.

The studies have shown that jaundice induces change in both renal and systemic vascular activity. There is decrease in vascular contractile responses and an increased endothelial derived relaxation factor (EDRF) found in obstructive jaundice\textsuperscript{23}. It has been stated that one of the causes inducing systemic hypotension is an excess in the amount of EDRF. There may be a relationship between the reported tendency to develop hypotension and the apparent predisposition to the development of acute renal failure in jaundiced patient. The amount of haemorrhage required to induce hypovolaemic shock was much less for jaundiced dogs than for non-jaundiced controls\textsuperscript{14}.

It is appreciated that, as a result of preoperative fluid depletion, jaundiced patients were more prone to the effect of hypovolaemic than non-jaundiced patients. Reduction in plasma volume in rats following common bile duct ligation was supported by Oms \textit{et al.}\textsuperscript{24} by the study of the fluid compartments within the body by using multi-isotope dilution techniques in bile duct ligated rats. They observed an initial reduction in the overall volume of extracellular fluid followed by 15 per cent fall in the plasma volume. The cause of volume depletion is appeared to be hypodipsia in association with impaired renal concentration of urine. They have also studied in human with similar reports.

At present, the pathogeneses of extracellular fluid depletion is not fully understood. Some studies point towards humoral mediators, such as atrial natriuretic peptide (ANP)\textsuperscript{24}. ANP is known to cause natriuresis to counter the action of water and sodium retaining hormones, to inhibit the thirst mechanism and to produce peripheral vasodilation\textsuperscript{25}. There is an increase in rabbit plasma ANP levels following common bile duct ligation, and this was associated with increase in the sodium and water retaining hormones, aldosterone, renin and ADH. Why ANP levels are inappropriately increased in the presence of a depleted extracellular space is not known. Perhaps release of ANP, triggered
by complete biliary obstruction, may be a primary event leading to isotonic extracellular volume depletion through hypodipsia, decreased appetite for sodium, and increased renal water and sodium losses. Neurogenic pathways from the liver to organs known to contain or release ANP (central nervous system, right atrium) may be involved but hepatic denervation did not prevent increased natriuresis after common bile duct ligation in dogs\textsuperscript{26}. ANP could be present in the liver and be released to the general circulation as a consequence of an increase in biliary or portal venous pressure following bile duct ligation.

We are now beginning to understand that the gastrointestinal tract is not a passive organ and that gastrointestinal dysfunction is not limited to only ileus or gastrointestinal bleeding. Instead, it is becoming increasingly clear that the gastrointestinal tract and its contents, including bacteria and their products such as endotoxin, may influence other organ systems and alter patient outcome. The gastrointestinal tract has important endocrine, immunologic, metabolic and barrier functions in addition to its role in nutrient absorption\textsuperscript{27}. Many investigators have documented that portal and systemic endotoxaemia are relatively common events in patients with obstructive jaundice. Although other explanations are possible, most investigators believe that it is the lack of bile salts reaching the intestinal lumen in patients with obstructive jaundice that results in the increased absorption of endotoxin into the portal circulation\textsuperscript{28}. The role of endotoxin is further supported by studies showing that preoperative treatment with oral bile salts prevent endotoxaemia and that, in patients so treated, postoperative renal function is maintained\textsuperscript{29,30}.

There has been increasing evidence that gut-derived endotoxins are the prime cause of renal dysfunction in obstructive jaundice. The effects of endotoxin are most likely to be mediated by the action of various cytokines. Cytokines are capable in altering renal haemodynamics and they have direct toxic effect on the kidney. They may alter renal haemodynamics by inducing a state of hypotension with concomitant release of vasoconstrictors\textsuperscript{31,32} and by redistributing intrarenal blood flow away from the renal cortex\textsuperscript{31}. The toxic effect of cytokines on the kidney may be secondary to their procoagulant activity, with induction of intravascular coagulation\textsuperscript{33}.

The Kupffer cells play an important role in removing any microorganisms in the portal blood, in inactivating endotoxin, and in clearing macromolecules or immune complexes\textsuperscript{3}. They also play a role in the removal of fibrin and fibrin complexes of high molecular weight in states associated with intravascular coagulation. Studies have shown impairment of Kupffer cell phagocytic function in obstructive jaundice, which promote spillover of endotoxin into the systemic circulation with subsequent development of systemic complications.

Indeed in both endotoxaemia and other states of disseminated intravascular coagulation, blockade of the reticuloendothelial system may result in renal cortical necrosis. Again intravascular coagulation is a dynamic process whereby procoagulant activity is countered by fibrinolysin and the latter may
be impaired in obstructive jaundice\textsuperscript{34}. Since endotoxaemia is related to the onset of renal failure in patients with obstructive jaundice\textsuperscript{3}, there have been studies conducted on the functional activity of the Kupffer cells on the liver in the several types of liver diseases\textsuperscript{3}.

Studies have shown that one of the main predictive factors of postoperative renal impairment and deaths is the presence of an increased preoperative level of serum bilirubin\textsuperscript{35}. Whether bile or its constituents have a direct toxic effect on kidney has to be investigated. Some investigators postulate that impairment of mitochondrial function by bilirubin results not only in decreased hepatic reserve as measured by glucose tolerance curve but in reduced renal function as well. It has been noted that mitochondrial sequestration of bilirubin occurs only when bilirubin distribution exceeds the binding capacity of albumin, which corresponds to in vivo concentration of bilirubin of >20mg/dl and albumin <3g/dl\textsuperscript{36}. Bilirubin has been shown to uncouple mitochondrial oxidative phosphorylation\textsuperscript{37}. Dawson\textsuperscript{38} has suggested that bilirubin may also induce renal ischaemia, but this effect has not been reproduced in other studies\textsuperscript{39}. Overall, there is insufficient evidence to implicate bilirubin in the pathogenesis of renal failure associated with obstructive jaundice.

\subsection*{3.2.b. RISK ASSESSMENT AND THERAPEUTIC STRATEGIES IN OBSTRUCTIVE JAUNDICE}

The recognition of renal dysfunction as a significant problem in patients with obstructive jaundice has led to the development of various theories about its pathogenesis and, based on these, to several proposed therapeutic strategies. Some of which have been widely used. The risk of postoperative morbidity and mortality in jaundiced patients is considerably higher than in non-jaundiced patients.

\section*{THERAPEUTIC STRATEGIES}

\textbf{Antiendotoxin therapy}

\textbf{Lactulose :} Lactulose, a commercially available synthetic disaccharide (galactoside-fructose), is used in the treatment of constipation and in the prevention of hepatic encephalopathy. Its exact mechanism of action in reducing endotoxaemia is not known but it may prevent endotoxaemia either by reducing or altering the gut flora, thereby reducing the endotoxin pool available for absorption, or by a direct effect on endotoxin itself\textsuperscript{40}. It may reduce the availability of colonic endotoxin for absorption by its laxative effect\textsuperscript{41}. Many of the toxic effects of endotoxin are mediated via the release from macrophages of effector substances such as tumour necrosis factor\textsuperscript{42}, and
lactulose has been shown to modify this macrophage response. It reduces endotoxin-related mortality and improves survival in bile duct-ligated rats, and a number of human studies have shown that preoperative administration of oral lactulose protects renal function in patients with obstructive jaundice. However, lactulose often produces diarrhoea, sometimes distressing, limiting its clinical usefulness.

**Bile salts:** Bile acids and salts have detergent properties and the endotoxin lipopolysaccharide molecule is susceptible to this action in vitro. In normal individuals significant systemic absorption of intact endotoxin is limited by emulsification or dissociation into non-toxic subunits. It has been suggested that the gut of patients with obstructive jaundice has depleted bile salts, which results in larger pool of endotoxin available for absorption into the portal circulation. Kocsar et al. showed that oral replacement of the bile salts reduces endotoxin absorption and mortality. The effect of bile salts on the gut flora is less certain.

In humans, the study of bile salts supplement has produced conflicting results. In Cahill’s study in 1983, patients receiving 48 hours prior to surgery had no portal or systemic endotoxaemia and none had evidence of renal impairment postoperatively. This was supported by more recent study of Pain et al. However, Gawley and Colleagues, who also used sodium deoxycholate observed impaired renal function, despite a reduction in endotoxaemia. Thompson et al. found no significant difference in endotoxaemia, renal function, morbidity and mortality between bile salt treated and control group. Theoretically, more than 95 per cent of sodium deoxycholate is absorbed in the terminal ileum, leaving only a small portion to reach into the colon. This means that only a small proportion actually reaches the major source to endotoxin, which is a major theoretical criticism of preoperative bile salt administration.

**Other antiendotoxin strategies**

Endotoxaemia has been stated as one of the causes of renal dysfunction in obstructive jaundice patients. Animal experiment of preoperative large bowel irrigation and administration of antiendotoxic compounds, such as polymixin B or taurolidine has shown some promise. A study of polymixin B in humans with obstructive jaundice has not proven to be beneficial. Till now there have no clinical trials using taurolidine in jaundiced patients, nor have there been any studies examining endotoxin antibodies in relation to obstructive jaundice and renal dysfunction.

**Biliary drainage**
A high serum bilirubin in jaundiced patients undergoing surgery is recognized as a predictor of morbidity and mortality and is associated with an increased frequency of renal insufficiency, septic complications and postoperative haemorrhage. Wait and Kahng postulated that, lowering bilirubin levels preoperatively might be beneficial. “External drainage” diverts bile away from the gastrointestinal tract whereas “internal drainage” returns bile in the gastrointestinal tract.

Gouma and co-workers, using a rat model, showed that endotoxaemia associated with biliary obstruction was reduced after internal drainage but was unaffected after external drainage. Percutaneous external biliary drainage has been criticized for being susceptible to local septic complications, which may account for persistent endotoxaemia. Other known complications resulted in a study are bleeding, bile leakage, sepsis and catheter dislodgment. Diamond and Rowlands, using modified form of external biliary drainage in a sterile model, demonstrated that both internal and external drainage are equally capable of reversing endotoxaemia.

Returning bile to the gastrointestinal tract has been assumed to be of benefit and in animal models has reduced postoperative endotoxaemia, renal impairment and mortality. Internal biliary drainage has also been considered to be important in the recovery of mononuclear phagocyte function. Whether the reversal of endotoxaemia has any significant benefit in preventing perioperative renal dysfunction is not entirely clear. Smith et al., however, demonstrated an improvement in renal function and fewer surgical complications in patients who had preoperative internal drainage. Percutaneously placed stents were subject to the same local complications as those associated with percutaneous external techniques. The result was that the overall incidence of associated morbidity negated any potential benefit. Speer et al. have demonstrated a lower thirty-day mortality rate for endoscopic stenting method of decompressing the biliary tract compared with the percutaneous technique and this method avoids the complications associated with percutaneous insertion. Although some studies have revealed fewer postoperative complications in patients who have undergone preoperative endoscopic internal drainage, principally a reduced incidence of biliary infection, bacteraemia and intraoperative bleeding, there are no specific data relating to renal function. A definitive answer about the efficacy of biliary drainage in preventing renal impairment requires further controlled trials.

**Perioperative dopamine administration**

Dopamine, an endogenous catecholamine, has a role of selective dilatation of renal vessels increasing renal blood flow, sodium excretion and glomerular filtration rate. These effects may be reproduced clinically by the infusion of low-dose dopamine hydrochloride (2-5 µg kg⁻¹ min⁻¹); this also causes
mesenteric, coronary and intracerebral vasodilatation. Intravenous dopamine infusion is currently used to maintain renal perfusion and urinary output in critically ill patients and those with sepsis. This treatment also reduces incidence of renal impairment in patients undergoing liver transplantation. Parks et al. conducted a study to assess renal dysfunction in patients with obstructive jaundice and found that perioperative dopamine administration (starting at induction of anaesthesia and continuing for 48 hours after operation) does not alter the incidence of postoperative renal dysfunction in jaundiced patients.

Mannitol

Mannitol is a sugar that is freely filtered by the glomeruli into the tubular fluid where it acts as an osmotic diuretic. The perioperative use of intravenous mannitol to protect renal function is widespread, with 84 per cent of consultant surgeons in the UK using it as some stage in the management of the jaundiced patients. The protective effect of mannitol in preventing deterioration in function in the ischaemic kidney was noted by many surgeons. Perioperative mannitol administration was advocated by Dawson in 1965 and has become the most widely used therapeutic strategy. The theoretical basis is that mannitol acts as an osmotic diuretic, increasing tubular production of urine so preventing occlusion by renal casts. The second basis is, as it passes through the renal tubule, mannitol may exert an osmotic effect and so prevent endothelial cell swelling. Third, it has been shown to increase renal blood flow. Fourth, it is an effective radical scavenger. Despite its widespread popularity, however, treatment with mannitol has been subjected to only a single prospective trial, which not only failed to demonstrate any significant benefit but also showed deterioration in renal function from the preoperative to the postoperative stage, which was actually greater in patients receiving mannitol. It also precipitated electrolyte disturbances. In their study mannitol group received 50g mannitol one hour before induction of anaesthesia which was continued for 2 days after surgery. Although, mannitol is able initially to improve the parameter, which is, monitored clinically, i.e. urine output, it might ultimately do harm and precipitate renal impairment.

Preoperative rehydration

Research has concentrated on control of fluid balance. Jaundiced patients are often fasted for prolonged periods before surgery for radiological
investigations. In addition, animals and patients with obstructive jaundice have a depleted extracellular fluid volume, thought to be due to hypodipsia, and an impaired ability to concentrate urine, possibly mediated via an increase in atrial natriuretic peptide\textsuperscript{70}. Such a predisposition to hypotension would be in keeping with the pathological changes of focal tubular necrosis that are often found in the kidneys when renal failure occurs in association with obstructive jaundice. Such a hypovolaemic state may be exacerbated by administration of an osmotic diuretic like mannitol. This has led to the concept of preoperative volume expansion, which in recent clinical studies have shown decreases in incidence of postoperative renal dysfunction and renal failure\textsuperscript{64}. It seems prudent that careful control of fluid and electrolyte balance in addition to volume expansion before surgical, endoscopic or radiological intervention may substantially reduce renal dysfunction and might prevent it almost completely\textsuperscript{70}. 